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Assessments of Chemical Mixtures via Toxicity Reference Values Overpredict Hazard to Ohio Fish Communities

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A diverse array of environmental data from Ohio were placed into a geographical information system (GIS). This GIS allowed for the investigation of approaches and paradigms currently advocated for ecological risk assessment. The paradigm of chemical mixture additivity was investigated in this project. Toxic units (toxic unit = concentration of a chemical in an organism/chemical concentration causing a specified effect) for 12 organic and 11 metal contaminants were calculated from 2878 fish samples collected at 1010 sites throughout the state of Ohio. Additive analysis of TUs for organic chemicals based on regulatory-based protective limits (toxicity reference value = USEPA water quality criterion*bioconcentration factor) overpredicted adverse effects to individual fish and fish communities. However, addition of organic chemical molar units did not overpredict adverse effects, thus, supporting the concept of baseline toxicity. Molar units of organic chemicals with diverse modes of action may be added together, so long as they are at concentrations below levels deemed protective of most species (e.g., 95%, water quality criterion). Analysis of metal TUs benchmarked against regulatory-based limits overpredicted adverse effects, whereas benchmark concentrations from population response (survival, growth, reproduction) data from the literature and Ohio reference site fish community responses corresponded better to field observations. Of the factors analyzed, habitat quality is the best single predictor of fish community integrity in Ohio, not body burdens of metals or organic chemicals.

Introduction

A current paradigm in environmental toxicology is that toxic units (TUs = concentration of a chemical in an organism/concentration causing a specified effect) of chemicals in mixtures are additive, particularly for constituents with the same mode of action (*1, 2*). In theory, a mixture of nonlethal concentrations of chemicals may add up to, or exceed, a toxic unit of 1, causing adverse organism, population and/or community effects. For organic compounds, the concepts of baseline toxicity (*3*−*6*) and critical body residues (*7, 8*) state that chemicals present in tissues at concentrations below levels that are associated with a specific mode of action may impart a narcotic mode of action despite any specific mode of action identified at higher concentrations. For example, an organochlorine insecticide present in tissues at 1/100th the LC_{50} may not be at a sufficient concentration to illicit a neurotoxic effect on fish, yet its presence in the fish may contribute to a generalized, narcotic mode of action. The additivity of effects from diverse metals in body residues has also been shown (*9*).

While laboratory-based evidence for these mixture toxicity concepts exists, their ecoepidemiological implications have been relatively untested. The primary reason is that few datasets exist which contain information on both contaminant concentrations in field populations and the ecological status of aquatic communities over a geographically extensive area. We have compiled such a dataset from Ohio Environmental Protection Agency sources, describing an extensive amount of information on aquatic habitat quality, fish species and community integrity, and contaminant residues in fish from locations throughout the state. The relationships of several additive approaches for organic and metal mixtures to in-field fish community responses (index of biotic integrity, IBI, percent fish with deformities, fin erosions, lesions and tumors, DELTs) were explored in this study. Relationships of IBI and DELTs to habitat quality were also studied.

Methods

Species and Lipid Data. Via electrofishing, the Ohio Environmental Protection Agency collected 2878 whole body or fish tissue samples from 1990 to 1996 at 1010 sites throughout the state of Ohio. Forty-three species, including hybrids, were obtained (Table 1). The most commonly sampled species were the following: channel catfish (*Ictalurus punctatus*); common carp (*Cyprinus carpio*); freshwater drum (*Aplodinotus grunniens*); largemouth bass (*Micropterus salmoides*); rock bass (*Ambloplites rupestris*); smallmouth bass (*Micropterus dolomieui*); white bass (*Morone chrysops*); and yellow bullhead (*Ictalurus natalis*). Tissue sample types included the following: SOF (skin on fillet, scaled—an individual fish), SOFC (skin on fillet composite, scaled—multiple fish of same species), SFF (skin off fillet, an individual fish), SFFC (skin off fillet composite, multiple fish of same species), and WBC (whole body composite, multiple fish of same species) (*10*). Seventy-eight percent of the samples had percent lipid determinations. The mean percent lipid per sample type per species was determined. The grand sample type mean (SOF, 0.65%; SOFC, 1.52%; SFF, 2.705%; SFFC, 2.84%; WBC, 4.88%) was substituted for samples in which the lipid percent was not known.

Tissue Toxic Units. Tissue residue data for metals and chlorinated organic compounds for fish captured by Ohio EPA were based on analyses of USEPA's priority pollutant list. Data were also available for base-neutral and volatile organic compounds; however, nearly all the tissue levels of these contaminants were below detection limits and thus were not used to analyze the toxicity of the mixture of organic chemical residues present in fish (see Supporting Information). Table 2 illustrates the chemicals available for mixture analysis.

The initial basis for an organic chemical TU was the toxic tissue screening concentration (TSC), a product of USEPA's water quality criterion and bioconcentration factor per respective chemical: TSC = WQC*BCF, Table 2 (*11*). This

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TABLE 1. Fish Species and Numbers of Tissues Sampled by Ohio EPA from 1990 to 1996[a]

sample types	species name	no. samples	mean percent lipid
SFFC, SOFC	Bigmouth Buffalo	1, 1	6.15, 8.09
SFFC, WBC	Black Bullhead	9, 3	1.02, 1.41
SOF, SOFC	Black Crappie	8, 25	0.51, 0.51
SOFC	Black Redhorse	5	1.73
SOFC, WBC	Bluegill Sunfish	11, 1	0.64, 2.54
SFF, SFFC	Brown Bullhead	9, 34	0.77, 0.68
SOFC	Brown Trout	3	2.27
WBC	Central Stoneroller	18	6.54
SFF, SFFC, SOFC, WBC	Channel Catfish	59, 180, 11, 3	3.94, 3.85, 5.11, 5.62
WBC	Com. Carp X Goldfish	2	9.00
SFF, SFFC, SOFC, WBC	Common Carp	9, 104, 59, 96	1.26, 2.94, 2.91, 5.91
WBC	Creek Chub	4	2.12
SFF, SFFC	Flathead Catfish	15, 5	1.06, 0.83
SOF, SOFC	Freshwater Drum	11, 89	1.35, 1.91
SOF, SOFC, WBC	Golden Redhorse	4, 15, 2	0.37, 1.32, 4.68
SOFC, WBC	Green Sunfish	3, 1	0.16, 2.54
WBC	Hornyhead Chub	1	5.88
SOF, SOFC, WBC	Largemouth Bass	35, 121, 5	0.54, 0.53, 1.94
SOFC	Longear Sunfish	7	0.54
SOF	Muskellunge	2	1.89
SOFC	Northern Hog Sucker	22	0.87
SOF, SOFC	Northern Pike	3, 5	0.24, 0.25
SOFC	Pumpkinseed Sunfish	2	0.32
WBC	Quillback Carpsucker	1	7.48
SOFC	Rainbow Trout	6	10.59
WBC	River Redhorse	1	0.94
SOF, SOFC, WBC	Rock Bass	17, 158, 7	0.34, 0.41, 3.13
WBC	Round Goby	2	1.78
SFFC, SOF, SOFC	Sauger	1, 8, 55	3.79, 0.71, 0.78
SFF, SOF, SOFC,	Sauger X Walleye	2, 18, 26	6.47, 0.59, 0.95
SOFC	Shorthead Redhorse	1	2.99
SOFC	Silver Redhorse	3	2.05
SOF, SOFC, WBC	Smallmouth Bass	50, 256, 5	0.88, 0.92, 3.85
SFFC, SOFC	Smallmouth Buffalo	1, 2	4.68, 4.95
SOF, SOFC	Spotted Bass	28, 35	0.34, 0.40
SOFC	Str. Bass X Wh. Bass	42	2.95
SOF, SOFC	Walleye	11, 87	0.70, 1.57
SOF, SOFC	White Bass	6, 119	1.56, 2.88
SOF, SOFC	White Crappie	19, 81	0.40, 0.66
SOFC	White Perch	62	5.99
SOF, SOFC, WBC	White Sucker	1, 15, 22	0.11, 1.33, 2.33
SFFC, SFF, SOFC, WBC	Yellow Bullhead	42, 11, 3, 5	0.53, 0.42, 0.79, 1.55
SOF, SOFC	Yellow Perch	1, 29	0.15, 0.31
	total no. samples	2242	

[a] Sample types include the following: SOF (skin on fillet, scaled—an individual fish), SOFC (skin on fillet composite, scaled—multiple fish of same species), SFF (skin off fillet, an individual fish), SFFC (skin off fillet composite, multiple fish of same species), WBC (whole body composite, multiple fish of same species) (*10*). Mean percent lipid concentrations are listed respective of sample type.

TABLE 2. Fish Residue Toxic Screening Concentrations (TSCs) Used To Calculate Toxic Units

chemical	Shephard TSC,[a] mg/kg	fifth %tile lit. TSC,[b] mg/kg	IBI-based TSC,[c] mg/kg	chemical	Shephard TSC,[a] mg/kg	fifth %tile lit. TSC,[b] mg/kg	IBI-based TSC,[c] mg/kg
aluminum	4.4	33		4,4′-DDT	0.054	0.47	
arsenic	1.6	1.7		chlordane	0.056	0.55	
cadmium	0.042	0.15	0.02 (18)	dieldrin	0.0090	0.22	
chromium	0.18	0.69		endosulfan (all forms)	0.0023	0.073	
copper	3.0	3.1	2.24 (4)	endrin	0.0091	0.025	
lead	0.064	2.2	0.09 (40)	hexachlorobenzene	32	0.49	
mercury	0.06	0.46	1.37 (55)	lindane	0.01	0.023	
nickel	0.39	18.4		methoxychlor	0.047	0.20	
selenium	0.56	1.1	0.26 (4)	mirex	0.018	0.020	
silver	0.37	0.27		PCB (all aroclors)	0.44	0.80	
zinc	20	27	26.98 (3)	toxaphene	0.0026	0.54	
4,4′-DDE	0.054	1.0					

[a] Reference *8*. [b] Corresponds to literature-based fifth percentile of effects residues, calculated from all single chemical laboratory tests focusing on community and population effects, such as mortality, growth, reproduction, behavior, and morphology. [c] TSCs were based on mean metals residue concentrations in fish sampled from fish communities with excellent IBI scores (≥45). Parentheses correspond to numbers of observations involved in the mean calculation.

product has been used as a toxicity reference value in screening level ecological risk assessments and is interpreted as a tissue residue in aquatic biota above which adverse ecological effects may occur. It is used here as the denomi-

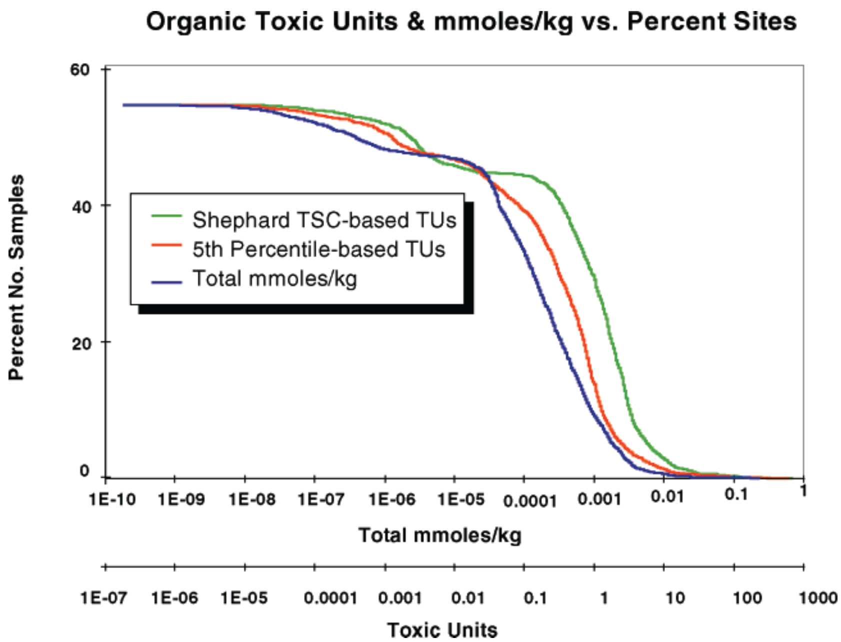

FIGURE 1. Distribution of mmol/kg and toxic units from organic contaminant residues in fish collected from 1010 sites in Ohio from 1990 to 1996.

TABLE 3. Summary of Stepwise Multiple Linear Regressions of the Index of Biotic Integrity (IBI) versus the Qualitative Habitat Evaluation Index (QHEI), Total Toxic Units for Organic Contaminants (Toxic Units), and the Total mmol/kg[a]

data set	dependent variable	step 1	step 2	final R^2
all sites ($N = 176$ segments)	IBI	QHEI (0.23, $p > 0.0001$)	− toxic units (0.002, $p > 0.52$)	0.24
	IBI	QHEI (0.23, $p > 0.0001$)	− mmol/kg (0.08, $p > 0.0001$)	0.31
sites with QHEI ≥ 60 ($N = 122$ segments)	IBI	QHEI (0.08, $p > 0.001$)	− toxic units (0.002, $p > 0.63$)	0.09
	IBI	QHEI (0.08, $p > 0.001$)	− mmol/kg (0.07, $p > 0.002$)	0.16

[a] Sign designation in front of the independent variables denotes slope direction. Values in parentheses represent coefficients of determination (partial R^2) per step and level of significance. Sites with QHEI scores of 60 or more are indicative of good to excellent habitat for fish communities.

nator in the TU calculation. Bioconcentration factors were obtained from the United States Environmental Protection Agency (*12*). For organic chemicals without BCF values in the USEPA report, BCFs were calculated via the equation

$$\log \mathrm{BCF} = (0.85 \times \log K_{ow}) - 0.70 \quad (\text{for } \log K_{ow} > 1.5) \quad (13)$$

This equation was derived from aquatic biota with a mean lipid content of 7.6%. According to USEPA (1980) (*14*), the mean lipid content of all aquatic biota is approximately 3.0%. All BCFs were normalized to 3% lipid for final TSC derivation. Water quality criteria corresponded to the lesser of the USEPA (1991) (*15*) freshwater or marine chronic ambient water quality criteria (AWQC), to derive a conservative TSC, a procedure commonly used in ecological risk assessments. Several TSC chemicals (e.g. PCB, chlordane, endosulfan, toxaphene) are mixtures of several isomers and/or congeners. Since the AWQC upon which TSC values were based on total PCB, total chlordane, and total toxaphene, the calculated TSCs for these chemicals were for total respective chemical residues. These TUs should be protective of 95% of taxa (*16*). Exceedence of 1 and 10 TUs are indicative of chronic (e.g., growth, reproduction) and acute effects (e.g., mortality) to >5% species, respectively, assuming an acute:chronic toxicity ratio of approximately 10 (*17*).

An alternate TSC was developed using a large literature review database where published papers relating measured whole body, wet weight tissue residues to adverse toxicological or ecological effects were compiled (*11*). A large subset of this database is publicly available as part of the Environmental Residue Effects Database (*18*) and can be accessed on the Internet at www.wes.army.mil/el/dots/dots.html. The literature database currently contains about 3400 records, of which 2500 are residue-effects information, and 900 are residue-no adverse effect data. The primary requirement for inclusion of a citation in the literature review was that it reportedly measured whole body concentrations of the chemicals discussed in the article. No limitations were placed on the route of chemical introduction to the biota: articles where the exposure was via water, sediment, diet, injection, or dermal application were all included in the literature review. Residue values derived from laboratory studies associating single chemical exposure with the lowest statistically significant adverse effect residue concentration observed in each publication were included in the review. The following endpoints were used in the derivation of adverse effects residue values: mortality, reproduction, growth, behavior, and morphological changes. Residues associated with effects on biochemical or physiological endpoints were not used nor were references which evaluated the toxicity of chemical mixtures. The fifth percentile of the rank ordered adverse

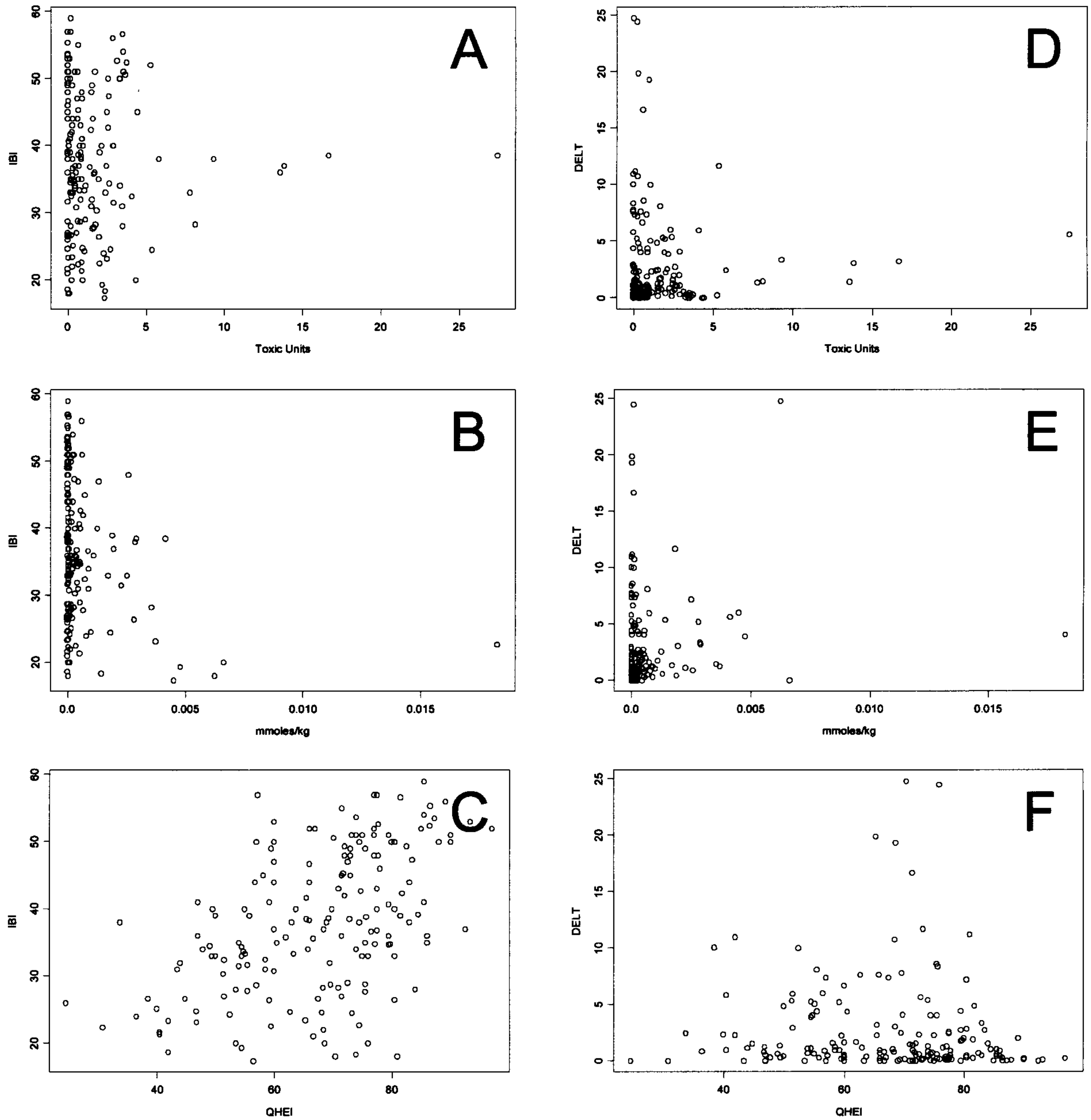

FIGURE 2. Relationships of the index of biotic integrity (IBI) to total organic contaminant toxic units (A), mmol/kg (B), and the qualitative evaluation index (QHEI) (C), at 176 river segments throughout Ohio. The proportion of fish with deformities, fin erosions, lesions and tumors, and other abnormalities (DELTs) versus total toxic units, mmol/kg, and QHEI are illustrated in D, E, and F.

effect residues for each chemical was determined and used as the alternate TSC (fifth percentile literature TSC, Table 2). The fifth percentile residue was selected because it represents a comparable approach to the original TSC yet is based on measured residue and adverse effects relationships. TUs for organic contaminants from captured fish were all normalized to 3% lipid content, per sample. A third method used for organic contaminants was the simple addition of molar units per tissue or body mass. The effect of lipid normalization on molar unit addition was also investigated.

Three approaches were also used for metals TU calculation. The first (TU = tissue concentration/TSC) used a TSC based on the geometric mean of measured BCF values and ambient water quality criteria set at a hardness of 50 mg/L $CaCO_3$. The second approach used is the fifth percentile of literature data for the alternate TSC, and the third approach was based on benchmarking metal residue levels in fish occurring in Ohio locations with excellent index of biotic integrity scores (IBI > 45). This last approach is only applicable for metals, which are ubiquitous and often essential.

Index of Biotic Integrity. The Index of Biotic Integrity (IBI) is a measure of fish community status, ranging from 12 (poorest) to 60 (best). The IBI is comprised of 12 metrics; each scored from 1 to 5. Example metrics include the following: total number of species, number of sunfish, minnow, intolerant and tolerant species, percent of round-bodied suckers, tolerant species, and omnivores (*19*). Included in the IBI is the metric: DELT, the proportion of individuals with deformities, eroded fins, lesions, tumors, and other abnormalities. DELT is used as an indicator of severe disturbances to the water quality and habitat of the receiving water. While the focus of this study was toxicological in nature, it is important to note that factors other than contaminants may affect IBI scores, such as habitat. As such, we also obtained habitat information (qualitative habitat

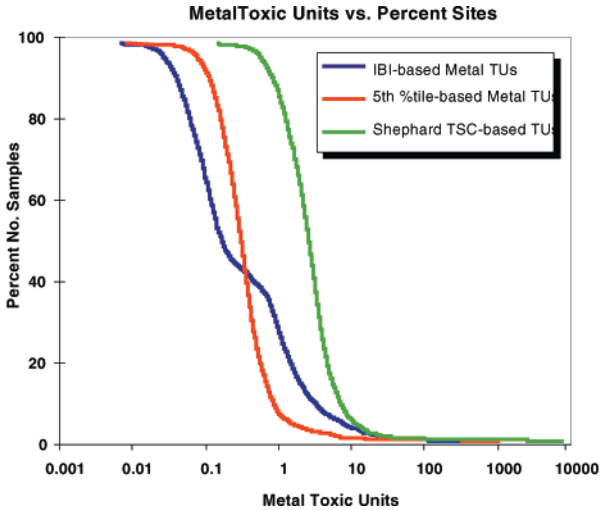

FIGURE 3. Distributions of metal toxic units from 1010 sites in Ohio (1990−1996), using three methods cited in Table 2.

evaluation index, QHEI) wherever possible. The QHEI is comprised of six metrics that sum to 100. The six metrics are as follows: substrate, instream cover, channel quality, riparian/erosion, pool/riffle, and gradient. Waters with QHEI scores of less than 45 can be considered limiting to aquatic life, while those >60 are considered good to excellent (*20*).

Data Integration for TU vs IBI, DELT, and QHEI Comparisons. Fish community, tissue residue, and habitat monitoring sites often did not occur at the exact same site (latitude and longitude). To bring these data into appropriate geographical proximity for direct comparison, several geographical information system (GIS) (ARC/INFO v 7.0.4, Environmental Systems Research Institute, Redlands, CA) and data management (MS-ACCESS v.7.0, Microsoft Corp, Redmond, WA) functions were used (*21, 22*). Of the >2400 samples from 1010 sites with residue data, 1262 metal samples and 1316 organic samples corresponding to 591 and 649 locations, respectively, were collected within 2 years of a comprehensive fish community analysis (IBI). Only these samples were used for TU or mmol/kg vs IBI and DELT comparisons. Of these locations, 746 metal and 609 organic samples were contained within 176 river segments, all inland of Lake Erie and the Ohio River, and were available for TU and mmol/kg vs IBI comparisons as well as IBI vs QHEI.

Background Metals Concentrations at Sites with Excellent Biotic Integrity. Excellent IBI scores for Ohio correspond to values of >45 (*19*). Via GIS and MS-ACCESS, the concentrations of metals in fish tissues at 56 excellent IBI sites were determined (Table 2). Most sites had concentrations of mercury and lead, while a few sites had data for cadmium, copper, selenium, and zinc. The numbers of observations involved in the mean calculation are also in Table 2.

Results and Discussion

We tested several additive concepts using fish tissue residue data from 2878 samples collected at 1010 sites throughout the state of Ohio. The sum of TUs for metals and organics as well as the sum of molar units for organics were compared to sum totals predicted to cause adverse effects and ecological data (IBI) for relevance. Using the Shephard TSCs (TSC = WQC*BCF) for organic contaminants, 29.4% of samples exceeded a TU of 1, while 3 and 0.3% exceeded TUs of 10 and 100, respectively. The TSCs adjusted to the fifth percentile of literature-based effects data caused a decrease in the total TUs such that 14, 1.4, and 0.1% exceeded TUs of 1, 10, and 100, respectively. The total number of mmol of organic contaminants/kg ranged from zero to 0.233 mmol/kg. Lipid normalization of molar units yielded a range of zero to 6.3 mmol/kg/lipid. Via the two toxic unit-based methods for organic mixture assessment, a substantial fraction of the fish sampled (14 to ~30%) should have come from populations experiencing some type of chronic effect. However, all of the samples were found to have approximately 0.2 mmol total chlorinated organics/kg or less (Figure 1) or ≤6 mmol/kg-lipid, indicating the estimated chronic thresholds (0.2−0.8 mmol/kg and 5 mmol/kg-lipid (*6*−*8*)) for narcosis, or baseline toxicity, had not been exceeded. (These thresholds were derived primarily via extrapolation from mortality data.) This conclusion appeared to be confirmed with the lack of correlation with either TUs or mmol/kg versus the index of biotic integrity (IBI) from 225 river segments. Further, there was no statistically significant relationship of either TU approaches or total molar units with the percent of fish having deformities, fin erosions, lesions, and tumors (DELTs). The lack of correlations indicate, however, that the ecosystem level threshold (HC5) of 0.25 mmol/kg-lipid (*6*) may be overly conservative.

For the 176 segments where residue, IBI, and instream habitat (qualitative habitat evaluative index, QHEI) were measured, there was a highly significant difference (*t*-test, $p < 6.5E\text{-}09$) between IBI scores from poor habitats (QHEI < 60) versus those from good habitats. The importance of habitat was further born out via forward stepwise multiple linear regression for IBI versus organic TUs, mmol/kg and QHEI (Table 3). Figure 2 illustrates the relationships of DELT and IBI to toxic units, mmol/kg, and habitat (QHEI). Twenty-three percent of the IBI variation at these sites could be accounted for by QHEI with an additional 8% by the total body burden of organic chemical expressed in mmol/kg. No significant additions were found for TUs. Segregating the dataset to include only sites with good to excellent habitat (QHEI > 60) effectively removed habitat as being an ecologically dominant factor in IBI variation, even though a highly significant 8% of the variation was accounted for by QHEI. As with the original dataset, TUs did not provide a statistically significant addition to QHEI effects, but organic chemical body burdens expressed in mmol/kg did provide a significant 7%, leading to a model addressing 16% of IBI variation. Habitat, therefore, appeared to be the dominant ecological factor in fish community health overall in Ohio, not body burdens of metals or organic chemicals. However, at sites containing good to excellent habitat, the relative importance chemical mixtures in addressing fish community health increased. Even so, it is dubious to overplay the statistical significance of mmol/kg as the vast majority of IBI variation remained unaccounted for.

Using Shephard's TSCs for metals, over 85% of all 2471 metals samples exceeded a TU of 1, while 5.4 and 0.6% exceeded TUs of 10 and 100, respectively (Figure 3). Revised TSCs based on fifth percentile of population level effects found in the literature resulted in fewer TUs. In this case, 27.5, 3.2, and 0.4% of samples exceeded 1, 10, and 100 TUs, respectively. TSCs benchmarked on metals concentrations found in fish from Ohio EPA containing robust and healthy fish communities (IBI > 45) resulted in a TU distribution between that of the two previous toxic unit distributions. At 305 river segments throughout Ohio, comparisons of toxic units versus IBI and DELTs were possible. In both cases, there were no statistical nor ecologically significant correlations (Figure 4).

The implications from this study are several. First, we demonstrated that the direct addition of toxic units is a conservative estimator of risk that may have little ecological relevance. This is particularly true when the toxic units were derived from water quality criteria intended to be protective of 95% of aquatic taxa. The problem is exacerbated as the numbers of chemicals added together increase (e.g., metals

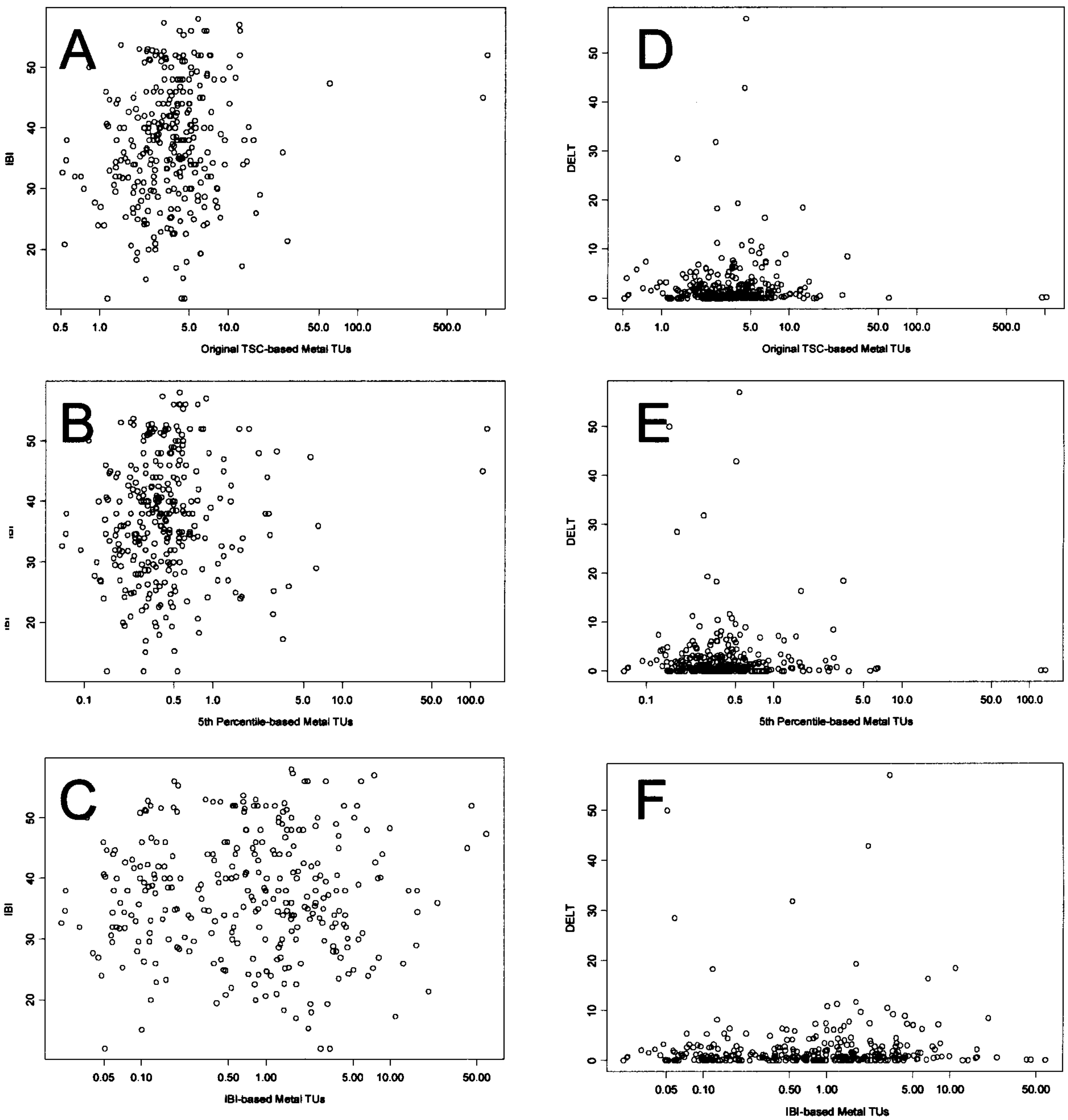

FIGURE 4. Relationships of metal toxic units vs index of biotic integrity (A, B, C) and proportion of fish with deformities, fin erosions, lesions and tumors, and other abnormalities (DELTs) (D, E, F).

TUs with organics, increased number of organic analytes, lower detection limits for existing analytes). Realistic risk assessments will require an integration of habitat factors into the risk characterization (*21, 22*). Second, in situations where low concentrations of organic tissue contaminants are present, addition of molar units appears to be a reasonable approach for organic mixture risk assessments, even for chemicals with diverse modes of action. The lack of correlation of mmol/kg vs IBI, and the lack of exceedence of mmol/kg as wet weight, or lipid normalized, not only did not contradict the previously established chronic thresholds but also did not support an ecosystem-level effects threshold estimate of 0.25 mmol/kg-lipid by Verhaar et al. (*6*). That is, a threshold lower than that for chronic toxicity was not determined. Even so, a more thorough test of this concept will require substantial numbers of samples that exceed the chronic toxicity and ecosystem-level toxicity thresholds. Third, extrapolation of effects via metal accumulation should take into account background concentrations from reference sites and the role of acclimation. Last, as stated by McCarty and MacKay (*8*), toxic events, where fish obtain a toxic dose of chemical(s), may more likely be found in situations where exposure is due to periodic, acutely acting pulses of chemicals. In these situations, toxicity will not be related to the overall body burden of tens or hundreds of chemicals but from the adverse dose from a single or small set of chemicals related to the pulse. If indeed this is the case, then obtaining appropriate residue data will have to conform to sampling strategies that specifically investigate pulse events.

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Supporting Information Available

Table of base neutral and volatile organic chemicals that were not detected in Ohio fish tissues. This material is available free of charge via the Internet at http://pubs.acs.org.

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